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HIDRADENOID VESTIBULOACANTHOMA.

Benign Neoplasia of Extra-apocrine Sites.

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In a recent article we discussed certain rare superficial neoplasms of the skin whose proliferating cells exhibit a sudoriferous metaplasia (Smith and Coburn, 1956). In them cellular matrices, often showing a pronounced multifocal arrangement, arise from immature rete cells by a process of " adnexal deviation". For this small group of neoplasms we suggested the generic term " hidroacanthoma simplex " because their major origin is from the rete, i.e. they are acanthomata, and because their adnexal differentiation is of sweat-glandular type only.

The neoplasms which we classify as hidradenoid vestibuloacanthoma differ from the foregoing in their more complex type of adnexal deviation. Within this group are benign and malignant neoplasms of solely extra-apocrine sites ; their clinical importance is considerable and they are well represented in two main tumour-bearing areas of the skin, namely the auriculo-facial region and the hands. A third type includes the hidradenoid vestibuloacanthomata occurring in the apocrine regions and in relation to heterotopic apocrine sweat glands. Our present purpose is to consider the benign neoplasms of extra-apocrine sites.

The Concept of Vestibuloacanthoma.

Each pilo-sebaceous follicle may be regarded as a vestibule with specialized outpouchings, the hair sacs and sebaceous glands. The stratified epithelium of the normal vestibule has a certain structural range. The squamous cells of its upper part resemble those of the contiguous epidermis but lower down they are paler and there is no granular layer. Thus, in the lower vestibule the maturation of the cells is simplified and merges imperceptibly with that of the adjoining hair sacs and sebaceous glands. A vestibuloacanthoma is an acanthoma in which the form of cell maturation corresponds with that of the vestibule. This basic vestibular pattern is often further modified by continuing adnexal deviation whereby primordial matrices of pilo-sebaceous nature are developed ; the degree and extent of this primordial metaplasia varies from tumour to tumour.

In most mammals the sweat gland is a third adnexal structure opening into the vestibule. In higher primates (chimpanzee, orang-utan) over half the sweat glands open directly on to the surface. In man this follicular linkage has become much more restricted and is only seen in apocrine gland areas. The hidradenoid nature of vestibuloacanthomata occurring in these apocrine regions is emphasised, as one would expect, and sudoriferous differentiation of their primordial matrices is often a marked feature.

Hidradenoid vestibuloacanthomata are also found outside apocrine sites. They may occur almost anywhere on the skin but are mainly confined to the head, hands and feet and certain specialized areas such as the groin, umbilical and sacro-coccygeal regions ; these sites of election are to some extent the reverse of those of hidroacanthoma simplex. The explanation of this " mixed " deviation appears to lie in the local quality of the skin ; the sweat glands seem to differ from the usual eccrine type in retaining a more primitive or " subapocrine " status. The tumours show two components—vestibular epithelium and sudoriferous matrices. Although the process still represents a neogenesis of sweat apparatus the new tubular glands emerge as a number of *hidro-vestibular complexes.*

That the two types of epidermal appendage (sweat glands and hair follicles) are not as different as the structure of postnatal skin would indicate, is suggested by their embryogenesis and by their neoplastic behaviour. The earliest adnexal structures to develop from the surface ectoderm are the *anlagen* of the follicles, appearing first in relation to the eyebrow, lips and chin. The sweat glands do not start to develop until the fourth month, first appearing in the hairless areas of the fingers, palms and soles and on the face. At this time the surface of the embryo is still covered by a very characteristic epithelium which is composed of clear cells with prominent approximated borders and small hyperchromatic nuclei (Fig. 1). This *clear-cell* epithelium is the parent tissue

for many follicles and sweat glands, certainly for those glands which form relatively early in ontogeny. Eccrine sweat glands arise directly from the surface epithelium. Apocrine glands always originate from the follicular vestibules though many later acquire an independent opening on the skin by an upward migration of their vestibular attachments. Steiner (1926) has stressed the frequency of this phenomenon and quotes Carossini (1912)

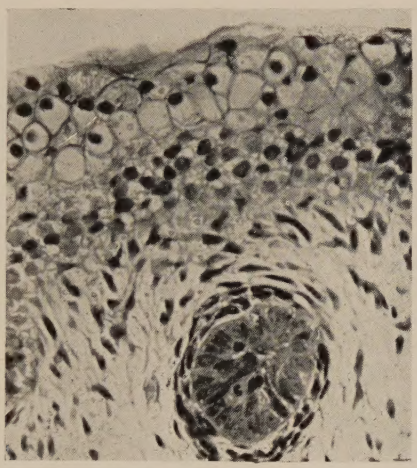

Fig. 1.—Clear-cell epithelium forming the surface ectoderm of a 14-week human embryo. Facial region. × 300.

who had reported such behaviour as being widespread ; this last author found sweat glands developing from the follicles in the thirteen skin areas he investigated. Schiefferdecker (1917 ; 1922) assumed that outside the normal apocrine areas a widespread retrogression took place of those sweat glands which arose from the follicles. This view was in accordance with his concept of the absolute division of sweat glands into apocrine and eccrine varieties in all their aspects. In this he was opposed by Brinkmann (1923–24) who, though freely accepting the Schiefferdecker subdivision, did not regard it as in any way fundamental. He did not regard eccrine sweat glands as something phylogenetically new but saw them merely as structures which had become loosed from the follicles during the course of evolution and adapted to the production of a watery secretion. Neither he nor Steiner saw any histological evidence of regression of the follicle-linked sweat glands. Steiner was also struck by the apparent disappearance of the large (apocrine) glands seen in the foetal inguinal region. Most anatomists have assumed that large, relatively advanced foetal glands of this type developing from the follicles are destined for an apocrine status, though as Borsetto (1951) points out the number of apocrine glands easily recognisable at birth may be small and they do not attain their definitive volume till 9–10

years in the female and 13–14 years in the male. In this delayed attainment of full function they resemble the sebaceous glands.

This derivation of seemingly eccrine sweat glands from vestibular epithelium can be correlated with the morphology of many subepidermal tumours. On the head, hands and feet the common sweat-gland tumour is of the " salivary gland " type. Tumours of the hair follicles can show extensive sweat-glandular

FIG. 2.—Sweat-duct differentiation in association with clear-cell epithelium. Subepidermal tumour of upper malar region. × 400.

differentiation as in some examples of epithelioma adenoides cysticum and cylindroma. Another important variety is that in which sweat gland differentiation is combined with clear-cell epithelium (Fig. 2). Histologically this clear-cell epithelium is identical with the surface ectoderm depicted in Fig. 1 and it may be regarded as the simplest example of a stratified epithelium, which in normal postnatal skin is limited to the outer zone of the hair sac.

Histological Subdivision.

Hidradenoid vestibuloacanthomata of non-apocrine nature may be divided into two general though not fully distinct categories—vestibulo-adnexal and

adnexal. As each of these categories contains both benign and malignant lesions the whole group is divisible into two series ; this parallels hidroacanthoma simplex. In tumours of the vestibulo-adnexal series the immature matrix cells still resemble the small cells of the rete and follicular vestibule ; in the adnexal series the matrices are formed by a new, non-epidermal type of basocellular epithelium akin to that of the follicular primordia.

Closely related tumours exist in which the sudoriferous metaplasia is very restricted in extent ; these constitute hidradenoid vestibuloacanthomata imperfecta, which in turn have many close relatives of a non-specific type among the seborrhoeic warts. Hence the subject matter of this paper is provided by three classes of neoplasm :

Overt hidradenoid vestibuloacanthoma.
Imperfect hidradenoid vestibuloacanthoma.
Non-specific vestibuloacanthoma.

Overt Hidradenoid Vestibuloacanthoma.

Vestibulo-adnexal Series.

All these neoplasms are characterized by a relative excess of matrix cells ; they are of solid build with a poor standard of sudoriferous differentiation.

The acanthosis occurs as a thickening and elongation of the rete ridges leading to an elevated tumour, which may form a localized papilloma or be more sessile depending on the lateral extent of the neoplasia and the looseness or otherwise of the underlying tissues. The scale is thickened, whereby the surface acquires a verrucose appearance, and the tumours tend to grow downwards, at least in part.

A substantial part of the new epithelium is formed by the immature matrix cells ; they occupy the basal regions and may be arranged in part as circumscribed nests. The matrix cells are small and sharply outlined, of uniform size and have narrow eosinophilic cytoplasmic rims with hyperchromatic nuclei ; their shape varies from angulated to spindle. As in the normal rete the cells maintain an even nuclear and cell spacing. Intercellular bridges are in the main well preserved except in relation to small areas of cell necrosis which may be widespread. The maturation of these small elements produces areas of larger squamous cells among which a patchy cystic necrosis occurs. The resulting lumina have mostly a non-specific character but some are like ducts, especially those lined by cuboidal cells. All these spaces contain basophilic cell remains ; haemorrhage into them is common. A few of these tumours give rise to small numbers of well differentiated lumina (Fig. 3); this seems to occur when downward growth is marked.

As a rule the paler vestibular epithelium is not well shown by these tumours ; when present it partly replaces the surface epithelium and may contribute to

the thick scale. Small numbers of epithelial pearls may be evident with or without hyalinized centres of keratin-like material. Variable numbers of hair shafts course through the neoplastic epithelium and are surrounded by thick horny envelopes.

Interpretation.—Both the morphology of the matrices and their appearance in part as circumscribed nests are strongly reminiscent of hidroacanthoma

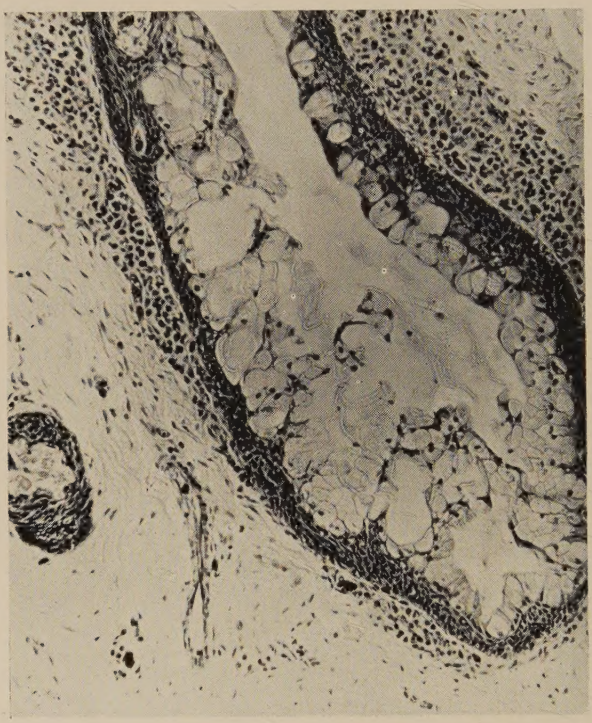

FIG. 3.—Verrucose hidradenoid vestibuloacanthoma. Large lumen lined by glandular cells. × 135.

simplex, the epidermo-adnexal forms of which are strict analogues of the present group. Distinguishing features of the matrices are their tendency to occur as accumulations in the basal regions rather than to be carried intra-epidermally and their association with vestibular epithelium. Cystic necrosis is a prominent feature of both groups.

The production of epithelial pearls indicates a flexibility in the range of differentiation, and depends upon a near-epidermal form of cell maturation; we regard these structures as homologous with the upper vestibule, not with the epidermis. They should not be confused with the cornified vestibules of pre-existing hair shafts which owing to the distortion of their course are often

seen in transverse section. The tumour matrices have the ability to differentiate into duct-like lining epithelia and into those intermediate grades of epithelium which we call vestibular : this maturation potential is expressed by the term " vestibulo-adnexal ".

Adnexal Series.

Here the matrices present a less uniform picture. They include immature cells with small hyperchromatic nuclei, whose cytoplasm is in general paler, scantier, and less well defined than in vestibulo-adnexal forms. These mature into larger cells with more plentiful cytoplasm and vesicular nuclei, often

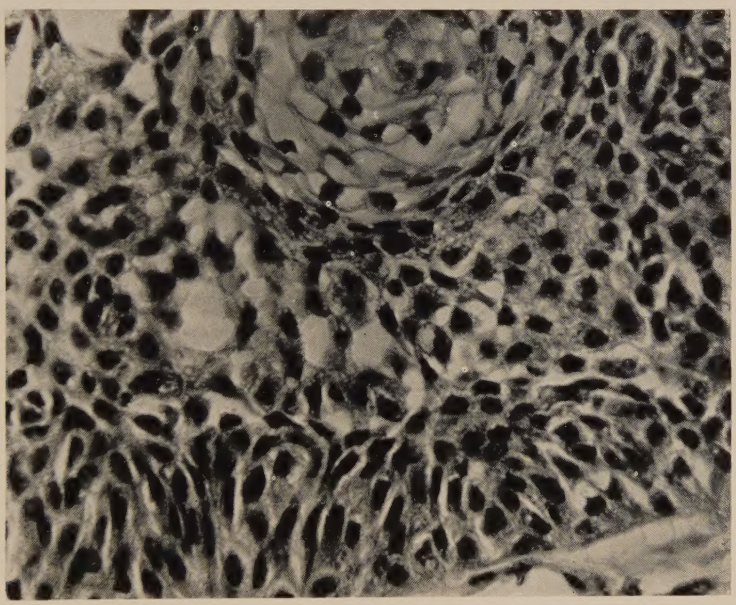

Fig. 4.—Adnexal matrix. Fine cytoplasmic vacuolation of immature cells. Face. × 400.

very various, some eosinophilic and others with foamy vacuolated cytoplasm. Even among the small cells this vacuolation may be obvious (Fig. 4) ; it often gives a semi-syncytial appearance, an effect which is enhanced by the tendency to crowding and erratic disposition of the larger vesicular nuclei. Among the matrix cells one sees large areas of clear-cell epithelium, whose cells have heavily delineated borders and generally retain a small hyperchromatic nucleus.

In many of these tumours a striking vacuolation of the cells is seen outside the matrix areas, mainly in the peripheral rete. In cells which are otherwise apparently of epidermal type a large paranuclear vacuole makes its appearance,

indenting and deforming the nucleus which may then appear in section as a ring. Similar changes are also seen in non-neoplastic conditions.

The organization of these tumours is dependent on a number of factors acting together. Two main structural types may be distinguished, suborganoid and organoid. The essential difference lies in the less solid character and more universal differentiation of the latter.

Suborganoid.—These are acanthomata with solid accumulations of neoplastic cells on their lower aspect. The site of origin of the main tumour mass from

FIG. 5.—Adnexal tumour with well differentiated though extensive duct spaces. Umbilical region. × 110.

the rete may be relatively localized, whereby the impression is given of a primarily subepidermal tumour though there are numerous points of continuity with the surface epithelium. The central acanthosis is usually of the "fused peg" type, the sudoriferous metaplasia affecting mainly its deeper portions. Differentiation produces spaces which are often extensive. Their lining cells are well formed (Fig. 5), mostly cuboidal and if of duct type often have a cuticular border; only rarely do they show apocrine features. Transitions exist between those spaces which have a properly differentiated lining and less specific areas of cystic necrosis; the former usually contain the vacuolated remains of necrotic cells and the latter clusters of surviving cells with plentiful vacuolated cytoplasm which lie scattered about in a loose fashion (Fig. 6). This tendency to cell individuation is seen outside the spaces and may be

pronounced in some areas ; it is also evident among the smaller matrix cells. Into such finely spongiose epithelium marked seepage of red blood cells can occur.

Clear-cell epithelium is often prominent in these tumours, sometimes extending up to the surface of the tumour, in place of the upper layers of the epidermis as in the embryo.

Interpretation.—There is a sharp contrast with the vestibulo-adnexal forms.

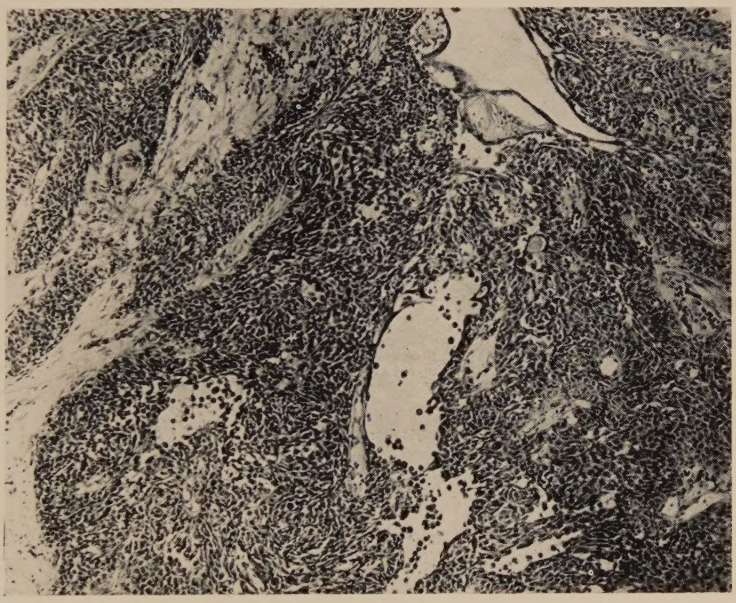

FIG. 6.—Same tumour as Fig. 4. Ill-formed spaces containing clusters of individuated cells and partly lined by duct epithelium. × 75.

(i) The matrix elements have diverged from the epidermal type ; although their morphology is variable they now resemble the less mature cells of normal pilo-sebaceous matrices.

(ii) Differentiation conforms with the enhanced adnexal deviation. The matrices of these tumours form well differentiated lumina and clear-cell epithelium, often in large amounts. This behaviour contrasts with that of vestibulo-adnexal matrices which as a rule produce barely recognizable sweat-glandular lumina and vestibular epithelium (pearls). Advanced differentiation is related to the rate of growth and downward extension of the proliferating epithelium. It tends to be lacking in early, and therefore superficial tumours and also in those where mitotic figures are comparatively numerous. Adnexal matrices do not produce keratin. There are no pearls and the only eosinophilic substance which may be found, apart from cuticular linings of new ducts,

is limited to a few eosinophilic spherules developing intracellularly (Fig. 7); these also are probably of a cuticular nature. Similar bodies are found in tumours of other tubular glands, e.g. salivary.

(iii) The downward growth tendency is exaggerated. This and the completeness of the adnexal metaplasia leads to some destruction of pre-existing vestibular channels and hair shafts. However, numbers of plugged vestibules often survive in the superficial regions when metaplasia is less complete; they tend to be preserved in lesions which have an intact hyperkeratotic surface.

(iv) Among suborganoid members of the adnexal series three sub-types can be recognized. These are in no way separate entities but merely the morphological expression of different modes of tumour evolution.

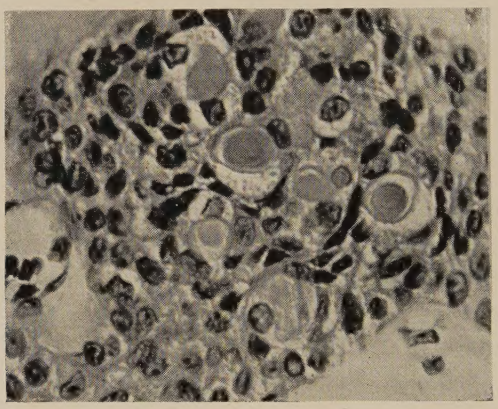

FIG. 7.—Hidradenoid vestibuloacanthoma. Intracellular eosinophilic spherules. Erratic spacing of matrix cell nuclei. Upper thigh. × 430.

In the first sub-type are those neoplasms whose adnexal deviation is less complete superficially. Their verrucosity depends on the vestibular and vestibulo-adnexal character of the upper epithelium. In the second sub-type sudoriferous metaplasia takes place at an early stage; as a consequence the upper zones of the rete are ultimately lost over the central tumour, though they may be replaced in part by clear-cell epithelium. The peripheral acanthosis is either plane or only slightly verrucose. Conventional classification does not cater for either subtype. Poorly differentiated and rapidly growing tumours would tend to be allocated to the transitional squamo-basal group—Krompecher's carcinoma cubo- or globocellulare, Darier's *epitheliome pavimenteux intermediare*. Gates, Warren and Warvi (1943), in company with other pathologists, classify "sweat-gland" tumours on morphological lines; they include in their "hidradenoma solidum" some hyperkeratotic tumours having several points of continuity with the epidermis.

The third sub-type includes tumours of frankly basocellular nature. The acanthosis is plane ; its peripheral extent may be considerable with the rete cells showing little abnormality, except for a sometimes pronounced paranuclear vacuolation. The continuity of the rete is abruptly broken by the new matrices, above which the surface is eroded. The neoplastic process may extend down the sweat duct, the matrices being partly split up by basophilic areas of cell necrosis. This process is well seen in the tumour shown in Fig. 8 where the formation of the narrow epithelial columns has been facilitated by the development of

Fig. 8.—" Basocellular " tumour of adnexal series. Non-specific and duct canalization. Leg. × 80.

these necrotic zones ; it also accounts for the strongly mucinous nature of much of the stroma. In addition a fine cystic necrosis is evident within the narrow epithelial strands producing a partial canalization ; some of the resulting lumina are unmistakably ductular, others less so.

The decision as to whether baso-cellular acanthomata are hidradenoid or not may be impossible if the matrices are not specifically sudoriferous but of a less differentiated type shared with other follicular primordia. This difficulty prevents any proper estimate of the incidence of the potentially sudoriferous lesions. In so far as basal-cell tumours have been adjudged to be adnexal in character the emphasis has been on their follicular nature. Thus, Haythorn (1931) recommended the adoption of the term " hair-matrix carcinoma ". However, Foot (1947), rightly in our view regarding all basal-cell carcinomata

as adnexal, recognized sudoriparous glandular in addition to pilar and basal-cell varieties.

Organoid.—The adnexal matrices arise in the usual manner from the immature cells of the rete and adjoining epithelium of the appendages but their subsequent disposition is along different lines, the resulting tumours being less solid and less compact than their suborganoid equivalents.

The rete ridges grow downwards as thin sheets of epithelium which have an open reticulate pattern, passing into a finely tubular arrangement (Fig. 9).

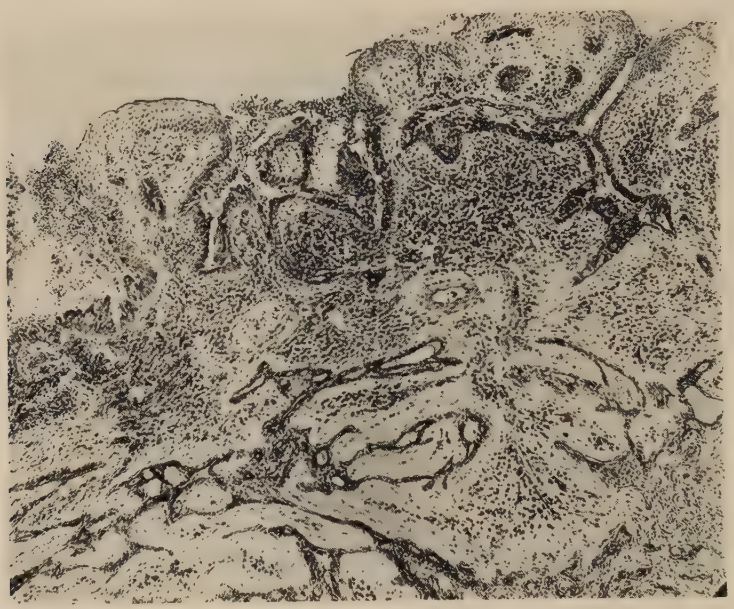

Fig. 9.—Organoid adnexal tumour. Finely reticulate and tubular structure. Ghost cells in some lumina. Scalp. × 67.

The duct spaces which form are small and narrow. An obvious tendency to individuation is evident among the smaller cells; apart from an apparent isolation of individual cells this leads to suprabasal splitting, which may be widespread in certain areas and at the surface may cause some exfoliation of the rete though a line of basal cells persists. Some erosion of the surface always occurs since the upper zones of the epidermis tend to be cast off as the adnexally deviated epithelium replaces the lower rete. Initially however there is an acanthosis with some hyperkeratosis.

Interpretation.—The more universal differentiation must be related to the method of growth, lumen formation being undoubtedly facilitated by the thinness of the downgrowing epithelium. The situation has its analogy in the solid suborganoid tumours where much of the differentiation adjoins the stroma.

Growth in organoid form seems to be favoured by the presence of a marked inflammatory cell reaction in the dermis, and the narrowness of the initial epithelial downgrowths can be attributed in large measure to mechanical factors. Chronically inflamed mucous membranes, such as the conjunctiva, produce similar pictures with epithelial downgrowths in which duct differentiation is common ; here, as in the organoid tumours of the skin, the earlier

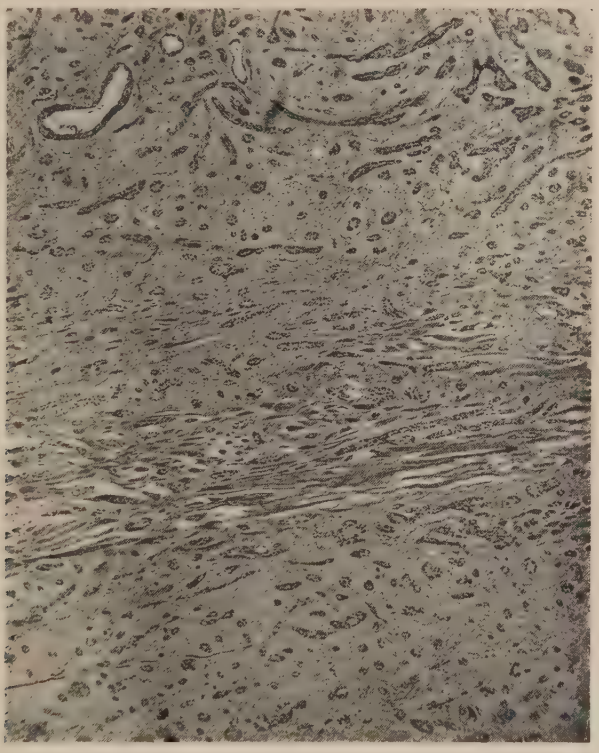

Fig. 10.—Morphoeiform basal cell carcinoma. Universal finely tubular structure. Forehead. × 40.

stages consist in reality of an upward displacement of the surface epithelium by the swollen papillae.

Cellular differentiation may, however, not be as good as structural and the quality of the cells bordering the new lumina may be poor. The best examples of this are to be found among the morphoeiform basal cell carcinomata, some of which take their main origin from the rete (Fig. 10). The explanation of this faulty differentiation is that for duct differentiation to occur a selective swelling and subsequent necrosis of the axial cells seems necessary—conditions which may not be realized. For the effective completion of this process the

more stable conditions obtaining in the solid tumours may be an advantage. Here differentiation occurs in relation to substantial masses of cells undergoing necrobiosis ; the resulting lumina are often large and erratically disposed and may be secondarily compressed.

A good example of an organoid tumour is the one referred to by Pinkus (1954) which arose from the side of the great toe in a negro. Branching sweat ducts with narrow lumina were lined by epidermal cells often with a definite cuticle. Pinkus classes this tumour as a naevus syringoadenomatosus papilliferus though he considered it unusual because of its eccrine nature. In our view such a tumour would not have either eccrine or apocrine status, but could be placed in an intermediate or subapocrine category. Most examples of naevus syringocystadenomatosus papilliferus are apocrine in nature. This title was used by Werther (1913) in describing a case of multiple tumours from the axilla and subsequent authors have adopted this terminology almost without exception. This is unfortunate because it has fostered the erroneous idea that the structure of these tumours depends on a papilliferous proliferation of intraduct epithelium, whereas the real mechanism consists in the elaboration of solid matrices in the rete and adjacent portions of the appendages with subsequent canalization. Some of the vestibular channels by which the new ducts communicate with the surface represent the mouths of pre-existing follicles. Connections with existing sweat ducts may be established. We believe that the basic structure of these organoid tumours is most simply and effectively expressed as hidradenoid vestibuloacanthoma. One overriding advantage is that they are at once placed in perspective with regard to the less universally differentiated lesions found in the suborganoid and imperfect classes. Pinkus himself has pointed out that naevus syringoadenomatosus papilliferus is commoner than is generally thought and that many microscopic lesions will be overlooked without serial sectioning. His available material included 17 fully developed lesions and 14 verrucose epidermal naevi. In 5 of the latter apocrine glands were absent. The lesson is that the final structure of any given tumour is only understandable in relation to the time of onset and progress of the sudoriferous metaplasia.

Imperfect Hidradenoid and Non-specific Classes.

The ubiquitous seborrhoeic wart is one of the commonest expressions of acquired neoplasia in the skin. The slightly augmented keratinization is the result of a minor disorder in the maturation of the rete cells which are of an epidermal type, though there is usually, except in some static tumours, an increase in the quantity of smaller rete cells. Characteristic are the horny invaginations which tend to be present in histological sections as sharply delineated cysts. Many of these are plugged follicular vestibules but others

are independent of the follicles and represent accumulations of keratin in the surface infoldings and their downward extension into the underlying epithelium. The non-follicular origin of many of these " horn cysts " was pointed out by Freudenthal (1926). The ordinary seborrhoeic wart is the simplest form of the vestibuloacanthoma—an acanthoma with vestibular plugging ; it is non-specific as it lacks primordial matrices.

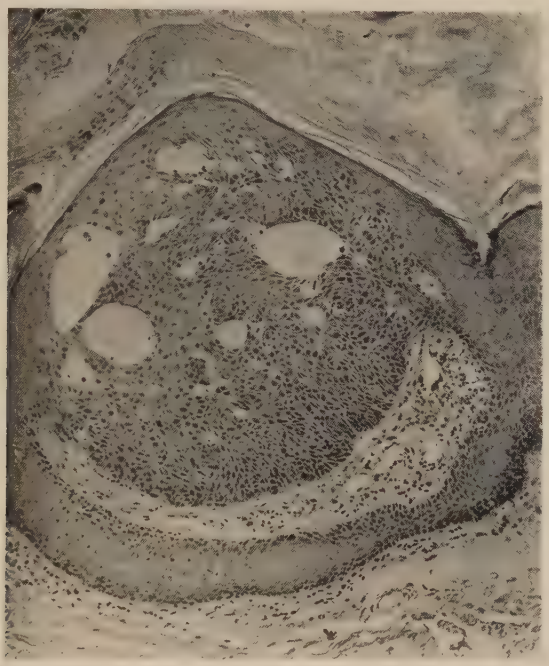

Fig. 11.—Seborrhoeic wart. Focal vestibulo-adnexal matrix. Eyelid. × 80.

Between these non-specific warty lesions and the overt hidradenoid tumours are numbers of imperfectly deviated examples. Recognizable adnexal deviation may be confined to very small portions of a tumour as a specially elaborated focus. Many seborrhoeic warts of the face, especially those around the eyelids, exhibit limited areas of sudoriferous metaplasia, usually of vestibulo-adnexal type (Fig. 11). A good illustration of adnexal deviation affecting seborrhoeic warts was a case exhibited by Kyrle (1915) to the Vienna Dermatological Society. A 48-year-old woman had multiple warts on the back ; at the base of some of them basal cell carcinoma of the Krompecher type had developed with resulting ulceration. Under the title of " Eccrine Poroma " Pinkus, Rogin and Goldman (1956) described five papular lesions from the non-hairy surfaces of the foot. All these tumours showed a marked overgrowth of the rete in which were inset some circumscribed masses of slightly smaller cells

which joined the epidermal cells but remained distinct from them ; within the confines of the smaller cells were numbers of sweat duct-like lumina. Solely on the basis of the sudoriferous matrix patterns (adnexal), as shown in the photographs, we would classify these five tumours as imperfect hidradenoid vestibuloacanthoma, of a subapocrine status. The derivation and the even arrangement of sweat glands on the palms and soles lends additional support to this contention, although secretory activity is predominantly eccrine in character. Romer (1898) was of the opinion that the regular arrangement of these glands indicated the previous existence of hairs and that they were the sole adnexal representatives of hair territories (Pinkus, 1905). Brinkmann (1910) was able to show in a small marsupial (*Chironectes variegatus*) that the sweat glands in these regions bore the same relationship to the hair discs as do the hair follicles themselves.

The existence of imperfect tumours showing abnormal rete patterns was one of the reasons which led Freudenthal to stress the atypical nature of facial warts. Becker (1951) has drawn attention to the presence in seborrhoeic warts of areas of abnormal proliferating cells suggestive of early cancer though the benign clinical course is quite opposed to any such concept ; he records an incidence as high as 40% in routinely sectioned tumours. A proportion of these abnormal cells would constitute areas of primordial metaplasia ; some would be hidradenoid.

The histological diagnosis of sudoriferous metaplasia rests primarily upon the presence of primordial matrices. Tumours of the vestibulo-adnexal series are not sharply divisible from non-specific varieties of vestibuloacanthoma owing to similarity of matrix pattern. Especially certain rapidly growing " basal-cell papillomata " with an excess of small cells in the deeper rete may be difficult to categorize. The existence of such problems in no way detracts from the general principle of adnexal deviation.

Finally it must be stressed that the general structure of the non-specific and imperfect classes is not fundamentally different from that of the overt forms. Even seborrhoeic warts, as Freudenthal (1926) has illustrated, may develop fine reticulate patterns reminiscent of the organoid tumours. Most seborrhoeic warts are solid growths ; their non-specific members link up, *via* vestibulo-adnexal forms, with the suborganoid tumours of the adnexal series. These three categories are contrasted in Table I ; the second sub-type is taken as representative of the adnexal series. The progressive augmentation or reduction of the various features may be noted.

Summary.

Hidradenoid vestibuloacanthoma is recommended as a term which can be applied to many superficially based neoplasms of the skin in which there is

TABLE I.—*Benign Vestibuloacanthoma.*

		Overt hidradenoid class.	
	Non-specific class.	Vestibulo-adnexal.	Suborganoid adnexal (2nd sub-type).
Matrix cells	Epidermal	Epidermo-mimetic	Basocellular
Verrucosity	+	+	−
Erosion of central tumour surface	−	−	+
Downward growth	+	++	+++
Destruction of existing follicles	−	+−	+
Follicular plugging	++	+	−
Vestibular epithelium	++	+	−
Clear-cell epithelium	−	+	++
Standard of sweat differentiation	−	+−	+
Incidence	++++	++	+

sudoriferous metaplasia. Such tumours have strong follicular associations, both as regards mode of origin and type of proliferating epithelium. Their cell patterns correspond to those found in the vestibules and primordial zones of the follicles, contrasting thereby with hidroacanthoma simplex whose matrix cells resemble those of the epidermis.

The existence of hidradenoid vestibuloacanthoma emphasizes the phylogenetic derivation of sweat glands from follicular vestibules. In the normal ontogenetic process many sweat glands arise from embryonic vestibular epithelium, and a proportion of these subsequently function in an eccrine manner. In this paper we have described those benign tumours whose differentiation is of this non-apocrine variety.

Overt examples of non-apocrine hidradenoid vestibuloacanthoma subdivide into two general categories, vestibulo-adnexal and adnexal, with related subtypes whose morphology reflects the time of onset and degree of the adnexal deviation. Tumours exist in which the sudoriferous metaplasia is restricted to small areas ; these imperfect forms represent elaborated seborrhoeic warts.

The main sources of these tumours are the auriculo-facial region, hands and feet.

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SAMUEL PLUMBE,
1795 to 1837.

R. M. B. MacKENNA.
St. Bartholomew's Hospital, London.

Recently Shelley and Crissey (1953) have correctly stated that very little is known of Samuel Plumbe, a man who, as Rosenthal (1937) wrote, " was imbued with an intense interest and zeal for his profession . . . and who emerged into the public eye only at intervals with publications of genuine worth and the highest scientific merit ".

Life History.

There are no Plumbe family records as such in the Berkshire Record Office, but the County Archivist informs me that Samuel Plumbe, bachelor and Molly Aldworth, spinster lived in the town of Wantage, Berkshire and were married by licence on 19 November 1794. Family records in the possession Mr. J. V. H. Plumbe of Woking show that this Samuel Plumbe was a wool merchant who lived in Mill Street, owned cloth mills and held contracts for the supply of cloth for greatcoats to the Army. On 8 October 1795 Molly Plumbe gave birth to the boy in whom we are interested ; the child was baptized into the Church of England in the Parish Church of St. Peter and St. Paul, Wantage, on 4 November of the same year. He was the firstborn of a large family for eventually he possessed five brothers and three sisters.

I have not attempted to discover where Samuel Plumbe received his early education, but presumably his parents continued to live in Wantage, for when he qualified in 1815 his address was given as " Wantage ". Scrutiny of the Pupil Dressers Book of St. Thomas's Hospital, London, shows that Plumbe was entered as a pupil dresser in that hospital on 14 October 1814. In the Dressers and Pupils Cash Book, 1811 to 1837, it is recorded that he had served an apprenticeship with " Mr. Stephen Wentworth Oxford ", which almost certainly means Mr. Wentworth of Oxford. At St. Thomas's on 10 October 1814 Plumbe paid eleven shillings to " the Surgeryman ", and £26 6s. 0d. entry money to Mr. Whitfield with whom he was entered, presumably as a pupil (Richard Whitfield was Apothecary to the Hospital and unofficial Secretary to the Medical School). Presumably Plumbe chose St. Thomas's Hospital because a relative (Alderman Samuel Plumbe, Lord Mayor of London 1778–79) had been President of the Hospital from 1773 to 1782.

In the Dedication to Sir Astley P. Cooper, Bart., F.R.S., which Plumbe wrote for his book (1824) he refers gratefully to " instructions long since received as a pupil " but Astley Cooper was appointed to the staff of Guy's Hospital in 1800, and I do not know whether Plumbe attended this famous surgeon at

Samuel Plumbe (*circa* 1830)

From a portrait in the possession of J. V. H. Plumbe, Esq.

Guy's, or at the Royal College of Surgeons (Astley Cooper was Hunterian Professor of Comparative Anatomy in 1814 and 1815) or as a private pupil.

Plumbe was admitted M.R.C.S. at the Royal College of Surgeons of London (as it was then called) on 6 October 1815. This was his sole diploma ; he had no university degree. From the printed lists of Members of the Royal College of Surgeons we learn that from 1816 to 1820 he served in the East India Com-

pany's Navy and then settled in practice at 65 Great Russell Street, Bloomsbury, London, in a house which (if the numbers have not changed in the last 137 years) stands at a corner site opposite the front of the British Museum. In those days it was a fashionable neighbourhood.

In 1822 he won the Jacksonian Prize of the Royal College of Surgeons with an essay " On Diseases of the Skin "; rather exceptionally the prize was also given to two other candidates—T. W. Chevalier for an essay " On Injuries and Diseases of Muscle " and G. Calvert who wrote "On Diseases of the Rectum".

Family papers in the possession of Mr. J. V. H. Plumbe show that Plumbe was married on three occasions. His first wife was Anne, by whom he had a daughter (Anne) ; his second wife was Emma Lloyd (or Lloydd) by whom he had four children (Samuel who eventually became an M.D. and practised in Maidenhead, Margaret, Emma and Henry) ; the third wife was Eliza who bore a son (Murray Kinnock). In the records of the Church of St. George's, Bloomsbury Way, it is recorded that Murray Kinnock was buried at the age of 7 weeks (Folio 259 : Burial No. 2110) ; the unusual name Kinnock may perhaps give a clue to Eliza's family. Despite much search in parish archives and at Somerset House I have not found any records of these marriages, nor of the birth or baptism of these children, nor—with the exception of Eliza and Murray —of any registrations of deaths or burials.

Plumbe moved from Great Russell Street ; the dedication (to Sir H. Halford, Bart.) of his essay on vaccination is dated 21 November 1830 and his address is there given as 7 Bedford Place, Russell Square. Thereafter he moved to 14 Southampton Street off Bloomsbury Square, only a very short distance from the house where Willan had lived. In 1939 Southampton Street was re-named Southampton Place, but Plumbe's house still stands, a three-storied red brick building, with a basement and dormer windows, steps leading to the massive front door which is flanked on each side by a rounded pilaster and having a pediment over the threshold.

In 1827 Plumbe was Surgeon to the Royal Metropolitan Infirmary for Children ; by 1830 he had become Senior-Surgeon there, but he resigned this appointment and at the time of his death was Acting-Surgeon to the Parochial Infirmary of St. Giles-in-the-Fields and St. George's, Bloomsbury. In 1824 he was a Member of the Medico-Chirurgical Society (of which Astley Cooper was once President) but had resigned by 1830.

Plumbe probably died at the age of 41 during the first six months of 1837. There is no entry of his death in the Registers at Somerset House, and enquiry there has failed to discover any last Will or Testament. All we know is that the dedication to Henry Hoare, Esq., of the last edition of Plumbe's text-book is signed by Plumbe and dated December 1836 ; the book appeared in 1837 and in a critique of this work published on 1 July 1837 in the *Medico-Chirurgical Review* (Vol. 27, p. 157) the writer refers to " the late Mr. Plumbe". It is just

possible that Plumbe died during the latter months of 1836, and post-dated the dedication; but this is unlikely for in several journals the book is reviewed in the summer of 1837, so that if Plumbe completed his manuscript by Christmas 1836 the printers and binders would have had the first five months of 1837 in which to finish their task and send the review copies to the editors. I cannot discover the circumstances of Plumbe's death. In the family papers it is stated that he died in London, in considerable difficulties because he had crippled himself financially by starting his brothers and sisters in life. The Librarian of *The Times* has been unable to trace any reference to his death in the files of that newspaper for 1837 and there is no such reference in *The Lancet* or in any other medical journal. Even in the *Medico-Chirurgical Review* the only reference (and that in a criticism of his last book) is " Mr. Plumbe . . . we regret to add the late Mr. Plumbe ". In those days obituary notices except of the great were brief, but in his day Plumbe was an acknowledged authority in London on tinea, his writings well known at home and abroad (P. Rayer in *Traité des Maladies de la Peau* (1835) has no less than 12 separate references to his work) and the extraordinary absence of reference to his death seems to imply that his last months or years were passed under some dark cloud of disapprobation.

On 18 November 1838 at 41 Great Russell Street a few doors away from his first house in Bloomsbury, Eliza " widow of Samuel Plumbe, Surgeon ", died of " inflammation of the lungs " aged 35 years and 11 months.

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1830 *A popular and impartial estimate of the present value of vaccination as a security against Small Pox, and of the danger of encouraging or tolerating the inoculation of the latter.* London: T. Cadell, Strand; Edinburgh: W. Blackwood. Post 8vo. Pp. 99.

1834 *An Address to the Governors of Christ's Hospital on the causes, and means of prevention of the disease called Ring-worm, in that establishment.* A pamphlet. London: Effingham Wilson, 88 Royal Exchange.

(I have called Demy 8vo any volume having pages approximately $8\frac{3}{4} \times 5\frac{1}{4}$ inches in size, and Post 8vo if the page size is approximately 8×5 inches.)

Notes on Plumbe's Work.

At the commencement of the Jacksonian Prize Essay, with evidence to suggest that Plumbe added the words when he wrote in the page numbers is "*Sat cito si sat bene*", the comma necessary after the second word being omitted. According to Roberts (1923) this is a quotation from St. Jerome, Epistle LXVI, para. 9 (Valler's edition) and is derived from Cato. It means "Quick enough, if good enough" and must be one of the most enigmatic distinguishing mottoes ever used in such a context. The scheme of the essay is that Plumbe suggests ten divisions of skin diseases, which he enumerates in the appendix, commencing with veruccae [*sic*] and ending with lupus. To some degree his text-book was an elaboration of his essay but with many differences, e.g. acne is considered towards the end of the essay but is dealt with early in the book. Nevertheless his important views on acne (vulgaris) are first stated in the Jacksonian discourse. This essay, despite its importance and its blithe contradictions of the beliefs of his eminent predecessors, has the appearance of having been quickly written, there being several erasures and a few blots. Plumbe evidently did not think it necessary to re-write a page if he made an error.

Porrigo (ringworm) was of great importance to Plumbe. On clinical grounds he attacked Willan's and Bateman's classification of six species of porrigo, bluntly stating "the first and last of these (p. larvalis and p. favosa) cannot be separated by any line of distinction founded on correct pathology". In regard to acne (vulgaris) he was the first properly to recognize that the a. punctata, a. simplex and a. indurata of Willan's and Bateman's nomenclature were "produced entirely by the ordinary progress of inflammation", and were not separate entities. His description of the manifestations of psoriasis is so important that Brian Russell (1950) supported the suggestion originally made by Bravo (1949) that, in recognition of the original delineators of the malady, the name Willan-Plumbe Syndrome should be adopted. Plumbe disapproved of the use of the pitch cap for epilation of the scalp and advised that "a pair of small forceps" should be used for this purpose; he recommended a similar procedure in the treatment of sycosis barbae. Rayer (1835) said that Plumbe's classification of skin disease was inferior to Willan's but that his book was remarkable for its practical views and for the importance which its author attached to the connection between cutaneous maladies and constitutional states. The first edition of the text-book was reviewed at length and not very sympathetically by an anonymous writer (possibly the Editor) in the *Medico-Chirurgical Review* (January 1825); *inter alia* the critic rather undeservedly deplores Plumbe's style and verbosity as well as his contradiction of some views accepted or preferred by his predecessors. Further he states "we have received severe strictures on Mr. Plumbe's work from more than one or two

anonymous sources. But of these we shall not avail ourselves as most of these bear the impress of the detestable *odium medicum* the disgrace of the profession . . . "

The fourth edition of Plumbe's book is the best. In an appendix he deals with many tropical diseases including yaws and Aleppo pustule, taking much of his information from the French school. An interesting paragraph may be quoted : " The engravings of Willan and Bateman have sunk into inutility, because of their enormous expense ". (Mr. L. M. Payne, Assistant Librarian to the Royal College of Physicians, informs me that the first edition of Bateman's *Delineations of Cutaneous Diseases* was published in 1817, the cost being £12 12s. 0d. The work was originally issued in twelve parts of which the first appeared in 1815 : each part sold for one guinea. Possibly some nineteen years later, when Plumbe made his comment, the cost of the Delineations had increased.)

It is worth noting that the second edition of Plumbe's *Essay on Ringworm* was " published by the author ". There is no indication in the first edition of his text-book that Plumbe was responsible for the business risks of its publication, but he may well have been for, on the title page, the exact wording is " Printed for Thomas and George Underwood ". This may explain why the names of no less than three different publishers are to be found in various editions of the book ; the words " printed for . . . " appear in each colophon.

The pamphlet on vaccination, which contains interesting statistics, was written because of " the utter forgetfulness or ignorance of the dreadful character and destructive consequences of the pest denominated Small Pox " and " to advocate the cause of Vaccination and stem the pride of prejudice against it ". It is a forceful and well argued document, from which one can deduce that in the public mind there was still confusion between vaccination and the inoculation of smallpox virus which Lady Mary Wortley Montagu (1689–1762) had advocated during her visit to Adrianople.

Plumbe's visit to Christ's Hospital followed the appointment of a Committee of eleven persons under the chairmanship of W. B. Tarbutt Esq., the Governors being perturbed because ringworm had " never been absent from the Institution for ten or twelve years or at the establishment at Hertford ". Plumbe found the scholars' diet deplorable and very tactfully said so, attributing much of the skin disease to this cause. The fare consisted of a frugal breakfast and supper, with small beer, and a big helping of meat at midday, occasionally followed by pease pudding. He found that the meat was boiled too much and in too large a quantity of water. He emphasized the danger of scurvy and added " the almost entire privation of vegetables tends to produce, if it be not the sole cause of the eruptive diseases reported on . . . " He recommends a liberal supply of vegetables, burning of caps, frequent examination and washing of pillow cases and ticking, isolation of infected boys, and the abolition of the

barbarous practice of cutting the hair close to the scalp on first admission. He makes two interesting comments : " London bread always contains alum, a powerful astringent, and capable of producing a tendency to constipation "; and " there is scarcely a school-boy in England who does not know what a ring-worm is on other parts of the body than the scalp, and who does not readily cure it by the application of ink ". (The ink used in Plumbe's day probably contained gallic acid and tannin (derived fom vegetable galls), ferrous sulphate, mucilage, and haematoxylin derived from logwood.)

One can but hope that Plumbe's visit to Christ's Hospital was welcomed by the pupils and at least was followed by some improvement in their diet.

Conclusion.

Plumbe was probably a sick man and knew his illness to be mortal when he wrote in the dedication of the fourth edition " That this book will live after us both, is my sincere prayer . . . ". But Plumbe's book did not live and is now largely forgotten. In his early days Plumbe was overshadowed by the titanic memory of Willan and Bateman, and after he died the rise of the continental schools and the publications of Erasmus Wilson, Tilbury Fox and Jonathan Hutchinson rapidly effaced his memory. But he served his generation better than many of his contemporaries would admit and because we have assimilated some of his views without knowing whence they were derived, we too are his debtors.

Acknowledgements.

I am greatly indebted to Professor J. H. Dible who, after the first draft of this paper was written, learned of the work and put me in touch with Mr. J. V. H. Plumbe of Woking the great-grandson of Samuel Plumbe by the marriage with Emma Lloyd ; Mr. J. V. H. Plumbe has very kindly allowed me to use family papers that are in his possession and to reproduce the portrait. I also wish to thank the following persons for their help :—

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ROYAL SOCIETY OF MEDICINE.

SECTION OF DERMATOLOGY.

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21 June 1956.

Essential Hyperlipaemia.—Dr. P. F. Borrie.

History.—A man aged 46 noticed 6 years ago the sudden appearance of exquisitely tender papules on his elbows, feet and trunk ; they varied in number and site from time to time but never cleared. His general health remained good and no other symptoms developed. His mother died of coronary artery disease at the age of 64.

On examination.—In 1954 he was found to be healthy but over weight. An eruption of yellow dome-shaped papules, varying in size from 1–3 mm. in diameter and surrounded by erythematous haloes, was seen grouped on the elbows, ankles and feet and scattered sparingly on the trunk. Pressure on a papule caused sharp, persistent pain. No other abnormalities were found.

Investigation.—The serum was opaque, settling into an upper layer of cream and a lower one of milk : total lipoids were 5590 mg. per 100 ml., phospholipoids 550 mg. and cholesterol 425 mg. Paper-electrophoresis showed a typical hyperlipaemic pattern. All other investigations were normal.

Treatment.

He was given 100 mg. heparin intravenously twice weekly for three months without effect. He was then given a 1000-calorie low fat diet and in 5 months the cutaneous lesions disappeared and have not reappeared since the diet was increased to 1500 calories.

Five months ago he was given phenylethyl acetic acid by mouth, 2 g. daily for 2 weeks and 3 g. daily for a month—an attempt to reduce his blood cholesterol which had varied between 230 and 400 mg. per 100 ml. for the previous 18 months, but rose while taking the drug to 660 mg. per 100 ml., returning to its previous level on stopping.

At the present time the serum is still milky, the total lipoid content being 2800 mg. per 100 ml., phospholipoids 560 mg. and cholesterol 320 mg.

Comment.

This patient shows the characteristic eruption of essential hyperlipaemia, the so-called eruptive xanthomata that occur in about half the cases. Other features of the condition, such as a familial incidence, hepatosphenomegaly, recurrent upper abdominal pain and hyperglycaemia, which only occur in a minority of cases, are not present.

Idiopathic Hypercholesterolaemic Xanthomatosis, with Hyperlipaemia.—Dr. P. F. Borrie.

History.—A man aged 47 noticed 5 years ago some yellow-red nodules on the elbows, followed by yellowing of the creases of the palms. His general health has remained good. His father suffered from xanthelasma.

On examination.—In 1954 he had typical tuberose xanthomata on the elbows and patchy yellowing of the creases of the palms. General physical examination revealed no other abnormalities.

The serum was milky : the cholesterol 550 mg. per 100 ml. Paper electrophoresis showed a hyperlipaemic pattern.

Treatment.

A low fat diet has not altered the eruption, but has reduced the milkiness of the serum. Phenylethyl acetic acid did not affect the blood cholesterol and the injection of heparin into the nodules did not reduce their size.

At the present time the total serum lipoids are 800 mg. per 100 ml., phospholipoids 435 mg. and cholesterol 210 mg.

Comment.

A typical example of idiopathic hypercholesterolaemic xanthomatosis. The presence of a raised serum neutral fat level has had no effect on the symptoms or signs, so a diagnosis of essential hyperlipaemia cannot possibly be made. According to Lever *et al* (1954) and Malmross *et al* (1954) however the presence of a milky serum due to an increase in neutral fat, makes the case one of essential hyperlipaemia, irrespective of the other symptoms and signs.

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Idiopathic Hypercholesterolaemic Xanthomatosis, with Hyperlipaemia.—Dr. P. F. Borrie.

History.—A man aged 47 noticed yellowing of the creases of the palms of his hands 7 years ago. Five years ago nodules appeared on his elbows and eighteen months ago on his buttocks. Eight months ago xanthelasma occurred on the upper eyelids. His general health has remained good. Six months ago his elder sister also developed xanthelasma.

On examination.—Xanthelasma of eyelids. Tuberose xanthomata of elbows and buttocks, yellowing of creases of palms. No other abnormalities.

Investigations.—The serum was clear up to June 1955, that is after the lesions on the buttocks occurred but before the xanthelasma. The cholesterol varied between 400 and 530 mg. per 100 ml. Paper electrophoresis showed a hypercholesterolaemic pattern. At the end of June 1955 the serum was first noticed to be faintly milky. In November 1955, after the xanthelasma appeared, the serum was obviously milky : total lipoids being 1600 mg. per 100 ml., phospholipoids 560 and cholesterol 420 mg. Paper electrophoresis showed a hyperlipaemic pattern.

Treatment.—A low fat diet, instituted before the advent of the hyperlipaemia, did not prevent its occurrence, nor has it had any effect on the cutaneous lesions.

Comment.

In spite of the milky serum, the physical signs and lack of response to treatment show this to be a case of idiopathic hypercholesterolaemic xanthomatosis. It is the first case in which hyperlipaemia has been seen to appear during the course of observation, but it is pertinent to note that this increase in serum neutral fat had no effect on the symptoms or signs.

Xanthomatosis and Leprosy.—Dr. W. H. Jopling and Dr. P. J. Hare.

Mr. W. H—, a coloured West Indian aged 28, lived in British Guiana all his life until he came to Britain in June 1955. One sister is said to have died suddenly from a " heart attack " at 25 years. He did not remember ever having had any illnesses, and there was no known contact with leprosy.

In July 1954 he first noticed a yellow-brown spot on his right arm, which was soon followed by another on his left arm, and during the ensuing twelve months a number of similar lesions appeared on various parts of the body and particularly on the arms. As the lesions enlarged they became raised above the general level of the skin. There was no irritation or scaling.

Since September 1954 he has suffered from recurrent pain in his left arm and associated weakness of the left hand, and since April 1955 he has had similar symptoms in his right arm and hand.

He was first seen in July 1955 and told us that he had not had any previous treatment. On examination he was found to have a good physique and to have no abnormalities in heart, lungs or abdomen. B.P. 140/80. Cranial nerves and tendon reflexes were normal.

Skin.—The lesions are about 30 yellowish plaques of various sizes, mainly on the arms, legs and back. Some of these have well defined edges ; others more diffuse consist of collections of small yellow papules on slightly hypopigmented areas. There are diffuse lesions over the elbows and knees and more clearly defined ones on the flexor surfaces of the arms. In addition the creases at the wrists show lines of small yellow papules. The chest, abdomen and face are exempt and there are no lesions on the tendons. Over some but not all of the lesions there is hyposensitivity to touch, temperature and pain.

Nerves.—Both ulnar nerves and the left common peroneal nerve are palpably thickened.

Muscles.—In both hands there is wasting and weakness of the intrinsic muscles supplied by the ulnar nerves, and there is weakness in dorsiflexing the left big toe.

Tests.—Serum cholesterol is 550 mg.%, but all the following tests are normal :

Full blood count, liver function tests, serum proteins and their electrophoretic pattern, W.R. and Kahn, urine examination, glucose tolerance curve and E.C.G.

The plasma is not fatty on inspection.

The lepromin test is negative and the tuberculin test is positive.

Smears from the lesions reveal a few acid-fast bacilli, and Dr. D. S. Ridley has reported on the histology as follows :

> " A skin biopsy revealed several masses of foam cells, with a few lymphocytes but no epithelioid or giant cells, which left clear a narrow zone beneath the epidermis. The few small nerve fibrils present were not infiltrated. Acid-fast bacilli were very scanty.
>
> " This was at first taken to indicate a burnt-out leproma and there is no purely histological reason to change this opinion. The emphatic absence of any history of treatment, however, taken in conjunction with an absence of bacilli in the foam cells, made that conclusion untenable. The possibility of xanthoma was therefore considered, suggested partly by the well-formed nature of the foam cells, and it was supported by the finding of a blood cholesterol of 550 mg. per 100 ml. It is probable that the foam cells do in fact represent xanthomatosis and that the extent of leprous infiltration in these lesions is slight."

One of us (P. J. H.) has demonstrated birefringence in the foam cell masses in a frozen section : the birefringence occurs in areas that stain for lipids with Oil Red. These findings suggest xanthoma rather than leprosy.

Comment.

This case demonstrates xanthomatosis occurring in leprosy.

A diagnosis of leprosy can be made on the strength of the neurological findings and the presence of acid-fast bacilli in skin smears.

The skin lesions do not show the central flattening characteristic of tuberculoid leprosy nor do they show the raised centres and ill defined edges of lepromatous leprosy. They could be considered consistent, however, with dimorphous (borderline) leprosy, except for their yellowness and the presence of lesions in the creases of the wrists—a most unusual site in leprosy.

The negative lepromin test is in keeping with a diagnosis of dimorphous leprosy.

Histology of the skin lesions is compatible with lepromatous leprosy after many years of treatment, but the patient has none of the clinical features of lepromatous leprosy and denies previous treatment. It seems more likely therefore, that the foam cells are xanthoma cells, and the fact that they are birefringent supports this conclusion.

We are indebted to Sir George McRobert for permission to show this case and to Dr. D. S. Ridley for the pathological reports.

Dr. P. J. Hare : At first sight there seems to be little in common between leprosy and xanthomatosis. Cases of lepromatous leprosy may be confused with xanthoma tuberosum ; if this seems an elementary confusion then those who are guilty of it are in the good company of Dr. Parkes Weber (1916) and Dr. Adamson (1922).

A histological similarity between lepromatous leprosy and xanthoma arises from the presence of foamy histiocytes in the dermis in both diseases. Points of distinction are the presence of abundant acid-fast bacilli in the foam cells of leprosy (unless the case has been intensively treated) and the birefringence of the foam cells in xanthoma when frozen sections are viewed with polarized light.

Cases have been reported in which both leprosy and xanthomata were present. The fullest description is that of Hopkins, Black and Ross (1939) who found an incidence of 11% of xanthelasma of the eyelids in over 200 cases of leprosy. Two of their cases also had xanthomatous nodules on the arms and a third showed a lepromatous lesion with a xanthomatous centre. They studied the serum lipids in their cases and claimed that hypercholesterolaemia was present in a proportion. They hypothesized that this might arise from liver damage due to leprosy, for although clinical and laboratory evidence of hepatic failure is rare in leprosy, leprous involvement of the liver is apparently very commonly found at autopsy. I feel, however, that their figures for blood cholesterol would now be accepted as falling within the limits of normal, if allowance is made for age (and they stressed that their cases were mainly in lepromatous lepers of middle age or over).

I think it cannot be denied that our patient has leprosy : there is thickening of the ulnar nerves with corresponding sensory and motor loss and acid-fast bacilli have been seen in skin biopsies. The lepromin test is negative, so that his disease is not of the tuberculoid type, and the histology is not what one would expect in the latter. Clinically, however, this is not lepromatous leprosy.

The serum cholesterol is 550 mg.%, and at first I was content to believe the skin lesions were purely xanthomatous ; in other words he had leprosy and, independently, hypercholesterolaemic xanthomatosis. Dr. Jopling, however, has demonstrated convincingly that some of the yellow lesions show definite sensory impairment. The lesions that are thus affected are clinically and histologically indistinguishable from the rest. It therefore seems probable that some of the lesions are both leprous and xanthomatous ; it can be argued that either the involvement of an area of skin by leprosy decided the site of formation of some of the xanthomata, or vice versa, since " trauma " localizes the lesions of both diseases.

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Xanthomatous Biliary Cirrhosis due to Reticuloendotheliosis.—Dr. Michael Feiwel and Dr. Thomas E. Oppe.

A male infant, born 20 August 1954, the first child of healthy parents. Pregnancy and delivery normal. Birthweight, 8 lb. 3 oz. Uneventful neonatal course.

At three months old he developed a rash on the trunk, front and back, of small evenly and sparsely distributed slightly scaling red maculo-papules 1–2 mm. diameter. The groins and the scalp were more profusely affected and the scalp was a little crusted. The distribution of the rash resembled seborrhoeic dermatitis while the individual lesions on the trunk suggested a guttate psoriasis or parapsoriasis. Each maculo-papule lasted about three weeks and healed leaving a faint white scar in some places.

A biopsy was done at nine months old.

Dr. P. L. Masters reported (17 June 1955).

" Microscopically the middle mm. or so of the epidermis is thickened and disrupted, its basal layer being ill-defined owing to infiltration of the epidermal-dermal junction by irregularly-shaped cells with moderately large oval or kidney-shaped vesicular

nuclei. No foamy cells or eosinophils are seen. The appearances seem consistent with Letterer-Siwe's disease but the small size and the broken-up character of the lesion make diagnosis difficult ".

Except for a poor gain in weight and the intermittent rash the child was well until nineteen months when he presented with jaundice of two weeks' duration which was associated with dark urine and pale stools. He was fretful with a poor appetite, but there was no fever or constitutional disturbance. Two small yellow nodules had lately appeared on the left cheek.

Physical Examination on Admission.

Small, mildly jaundiced. Weight 18 lb. Scaling and crusting areas on scalp with a few small papules on the trunk. No haemorrhagic lesions. On the left cheek are two pin-head sized xanthomata. Liver enlarged three finger-breadths below costal margin, firm, not tender. Spleen just palpable. No superficial lymphadenopathy.

Urine.—Urobilinogen 1·05 units %. Bile salts ++. Bile pigments ++.

Stools.—Light brown, stercobilin present, excess fatty acid crystals.

Liver function tests.—Serum bilirubin 2·2 mg.%. Thymol turbidity, 6 units. Total protein, 6·7 mg.%. Serum alkaline phosphatase, 95 King Armstrong units.

Chest skiagram.—" Diffuse micronodulation throughout both lung fields ".

Skeletal survey.—Normal.

At laparotomy no extra-hepatic cause for biliary obstruction was found. Dr. P. L. Masters reported on the specimen from a needle biopsy of the liver, 15 May 1956:

" Microscopically the liver shows considerable fibrosis and proliferation of bile-duct epithelium. No excess of reticulo-endothelial cells and pigment is detected. The changes are those of biliary cirrhosis ".

The serum was submitted to filter-paper electrophoresis and stained for proteins and lipoproteins (Dr. W. G. Dangerfield):

" The fresh serum which was a clear yellow shows a dense band of γ_1- or β_2-lipoprotein. This band extends from a position of a little ahead of the line of application 0 up to the front of the β-globulin. The serum after freezing was very turbid and gives a dense deposit at the site of application and a weak band level with β-globulin, probably β-lipoprotein. No α-lipoprotein can be detected in either strip ".

Chemical analysis.—Total lipoids, 5500 mg.%. Total cholesterol 1400 mg.%, mostly in free form. Phospholipid 3000 mg.%.

Progress.

The jaundice fluctuated and has gradually lessened. There was considerable pruritus and disturbance of sleep but the itching has also become less. The liver is firmer and dilated veins have appeared on the anterior abdominal and thoracic walls. The facial xanthomata are more prominent and further yellow xanthomata are appearing on the back and in the creases of the palms. The original rash has disappeared except for a few small crusts on the scalp. Weight is maintained.

Treatment.

Since 10 April 1956, he has been on prednisone, first 5 mg., then 10 mg., daily. Dietary fat is reduced.

Discussion.

The combination of skin lesions, pulmonary infiltration, hepatomegaly and failure to thrive, beginning in early infancy, strongly suggests a reticuloendotheliosis. The skin biopsy was compatible with the diagnosis, but it cannot be considered proved without further manifestation of the disease or the certain histological demonstration of abnormal cells. The resemblance of the rash in reticuloendotheliosis to seborrhoeic dermatitis has been mentioned by Wallgren (1940), Christie *et al.* (1954) and Lightwood

(1955) and it becomes purpuric if the disease is acute. Although the rash was sparse in our patient it was fairly characteristic.

Reticuloendotheliosis of early onset generally runs an acute course with involvement of liver, spleen, lymph glands, skin, lungs, bone marrow and skeleton and has a poor prognosis compared with that of later onset and granulomatous lesions of bone. In our patient the sites of reticulo-endothelial proliferation appear to be mainly in the liver, lungs and skin. Recoveries from Letterer-Siwe disease have been reported (Lightwood and Tizard, 1954). The relatively slow course in our patient would therefore be compatible with this diagnosis.

Jaundice, biliary cirrhosis, hyperlipaemia and skin xanthomata are unusual clinical features in the reticuloendotheliosis of infancy. Biliary cirrhosis from histiocytic infiltration and fibrosis of the portal tracts has been recorded by Karlen (1952), MacDonald and Shanks (1954), Case 2 ; Christie *et al.* (1954), Case 3 ; and Weidman and Freeman (1924), Case 2. In his classical paper on the systemic reticulo-endothelial granuloma Wallgren (1940) describes a case (2) where, at autopsy, large glands were found at the porta hepatis obstructing biliary flow. Intra- and extra-hepatic bile-duct obstruction are therefore possible sequelae of these disorders.

In biliary cirrhosis there is a hyperlipaemia characterized by raised serum phospholipid and free cholesterol values, but normal or slightly elevated neutral fat values. Ahrens and Kunkel (1949) have shown that a relationship exists between the degree of elevation of serum lipoids and the development of skin xanthomata. If total lipoids remain above 1800 mg. per 100 ml. for several months, skin xanthomata may form. Biliary cirrhosis is seen as a primary disease only in middle-aged women, but it has been described in childhood secondary to congenital atresia of the bile-ducts. Ahrens *et al.* (1951) describe four such patients, all jaundiced from birth or the first four days of life. It is interesting to note that skin xanthomata did not appear until the children were $1\frac{3}{4}$, $3\frac{1}{2}$, $1\frac{1}{2}$ and 1 year old. In our case skin xanthomata arose at the same time as clinical icterus when the infant was $1\frac{1}{2}$ years old. Soon after, a figure for total serum lipoids of over 5000 mg. per 100 ml. was found, but we have no knowledge of how long hyperlipaemia had existed. These xanthomata may be either the expression of the xanthomatous phase of the reticuloendotheliosis or secondary to raised serum lipoids.

A xanthomatous stage with foam cells and Touton giant cells is part of the histopathological picture of reticuloendotheliosis. Bodian (1955) says that the xanthomatous lesions do not essentially differ from the non-lipoid type of histiocytosis or from the eosinophilic granuloma of bone, all are simply stages in the evolution of a single type of lesion, the histiocytosis. Thannhauser (1950) makes a clinical distinction between the xanthomata of reticuloendotheliosis and those of biliary cirrhosis. The former have petechia-like lesions, corresponding to the early rash in our patient, and xanthomata disseminata. The latter have xanthomata tuberosa et plana ; although he admits that the xanthomata cannot always be distinguished clinically. We have not done a biopsy of a later nodule. The histology would have helped as the tuberous and plane xanthomata do not show the histiocytes and inflammatory cells present along with foam cells in disseminate xanthomata. In the absence of clinical certainty the more attractive hypothesis would link the two distinct cutaneous pictures in our case with two distinct processes, reticuloendotheliosis and the biliary cirrhosis ; our case would have two of Thannhauser's " Lipidoses ", with normocholesterolaemic and hypercholesterolaemic xanthomatoses.

The fact that no jaundice occurred at birth and no cause of extra-hepatic biliary obstruction was found at laparotomy excludes other causes of biliary cirrhosis such as partial atresia of the bile-ducts, haemolytic disease of the new-born with inspissated bile and choledochal cyst. The negative W.R. and tuberculin reaction exclude syphilis and tuberculosis. The pulmonary infiltration seen in the skiagram corresponds to reticuloendotheliosis, but at that age tuberculosis and in endemic areas histoplasmosis would have to be considered.

The high plasma lipoid values found in biliary cirrhosis are believed to be due to over-production by the damaged liver rather than due to retention from biliary obstruction. Electrophoretic studies of the serum proteins in patients with biliary cirrhosis (Sterling and Ricketts, 1949; Kunkel and Ahrens, 1949; Lever and MacLean, 1950) all showed considerable increases in the β globulin components suggesting an excess of β lipoprotein. Dr. W. G. Dangerfield, using filter-paper electrophoresis and staining for lipoproteins with Sudan black in 55% alcohol (Dangerfield and Smith, 1955) obtained the dense band of γ_1- or β_2-lipoprotein. Russ, Raymunt and Barr (1956) have investigated the lipoproteins in the plasma of a woman with biliary cirrhosis. They say that most of the lipoids are combined atypically with β globulin as low density β lipoproteins. Gofman flotation analysis demonstrated that molecules within the S_f 10–20 classes formed the major portion of the spectrum and in far greater concentration than seen in atherosclerosis, but chemical analyses showed that the lipoproteins, despite their similar flotation rates, differed from those in atherosclerosis. The instability of the abnormal lipoprotein is illustrated in our case. The bile-stained serum was clear as is the serum of other cases of xanthomatous biliary cirrhosis. On freezing an irreversible change took place and the serum became milky and showed a different lipoprotein pattern. By acting on sera from cases of biliary cirrhosis with a lecithinase derived from *Cl. welchii* Ahrens and Kunkel (1949) rendered them turbid and concluded that it was the high phospholipid constituent of these sera that held the serum lipoids in solution. They noted that their cases of primary biliary cirrhosis at autopsy were relatively free of atherosclerosis in contrast with patients with nephrosis, hypothyroidism or essential xanthomatosis who had a high incidence of premature atherosclerosis. In the latter cases the cholesterol rather than phospholipid is raised.

Unfortunately the architecture of the liver has probably been irreparably damaged in our patient and so hepatic failure or portal hypertension with haemorrhage will supervene even if the reticuloendotheliosis were to regress. The value of cortisone in other cases without liver damage has not been certain.

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Lipoatrophy, Gigantism and Hyperlipaemia with Xanthomatosis and Acanthosis Nigricans. Dr. J. A. Davis and Dr. M. Feiwel.

Susan C— (now 5 years old) was a normal healthy child (except for a mild left-sided congenital hemiplegia) until she was a year and 8 months old, when, after successive attacks of measles and glandular fever, she lost all her subcutaneous fat, including that on face, and began to grow with undue rapidity. Examination at that time revealed hepatosplenomegaly and generalized enlargement of lymph glands. In the next

three years she continued to grow very rapidly and at the age of 4 was as heavy and tall as an average child of 9 and had a bone age of 12. Her hair, which had previously been straight and fair, became dark and curly six months after the onset of her illness, and at about that time she had symptoms that suggested diabetes insipidus although she was able to concentrate her urine if deprived of fluids.

At 3 years old she had the first of a series of attacks of abdominal pain and transient xanthomatosis : the xanthomata were lentil-sized orange-red papules distributed around the shoulders. At the same time she developed acanthosis nigricans in the folds of the neck, axillae and groins, around the umbilicus and in the ante-cubital and popliteal fossae. At present her general health is satisfactory ; she has no symptoms ; and her I.Q. is 112. There are no signs of sexual precocity.

Investigation.

Serum.—Consistently lipaemic, the increase being in neutral fat and phospholipids and not in cholesterol. Total lipoid 1150 mg.%. Cholesterol 180 mg.%. Phospholipid 435 mg.%.

Serum electrophoretic pattern.—Normal.

Blood sugar curve.—Normal.

Urine.—Normal except for moderately consistent hypercalcuria. No glycosuria. 24-hour ketosteroid excretion 0·9 mgm.

B.M.R.—64 calories per sq. m. per hour, i.e. considerably raised.

Respiratory quotient.—Consistently 0·87.

Biopsy of skin.—No subcutaneous fat.

Biopsy of lymph gland.—Endothelioid hyperplasia and slight subcapsular and hilar fibrosis.

Skull skiagram.—Normal.

Ventriculogram.—No abnormality detected.

Comment.

This child appears to suffer from what Dr. R. D. Lawrence called " Lipoatrophic Diabetes " but in fact she has no diabetes, though this may develop when growth ceases. The attacks of abdominal pain and xanthomatosis resemble those that occur in the course of established hyperlipaemia in adults ; such cases also have an increase in serum neutral fat without hypercholesterolaemia.

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Discussion.

Dr. R. D. Lawrence: This is a very fascinating case ; I have seen a few all over the world and they are cropping up more and more. This disease occurs some years before they get diabetes. It is fundamentally an inability to store fat anywhere. That seems to lead to lipaemia, skin manifestations of xanthomatosis, to hepatomegaly, and sooner or later quite a severe diabetic state. The last, if one can explain it, is due to the impossibility of fat being laid down anywhere ; as we know the ultimate action of insulin in carbohydrate mechanism is not only to make sugar available but to store it as fat and when that cannot happen it is thrown back into the system and we have " diabetes ".

This child has the usual high basal metabolic rate ; I think I was told it was probably plus 30. Some of them develop this stage and diabetes a few years later.

Dr. Feiwel : The heparin-activated lipaemia clearing system has been more fully analysed by recent work. A lipoprotein lipase appears to be present in subcutaneous tissue and may as one of

its functions be responsible for liberating fatty acids from the serum lipoproteins and allow the deposition of fat-stores in the subcutaneous tissues. In this case the enzyme may be defective or absent resulting in inability to lay down fat. Perhaps this enzyme system is also defective, but in another way, in the essential hyperlipaemia syndrome.

Dr. LAWRENCE: I think that is correct. I postulated years ago that there must be some enzyme or hormone system which lays down fat (I called it a lipopesic factor) of which we are completely ignorant.

The PRESIDENT: There is considerable skeletal growth, which with the acanthosis nigricans suggests an abnormal pituitary activity.

The following papers were read and have been published in *Proc. R. Soc. Med.* **49**, 1065.

Lipoid Electrophoresis Patterns in Xanthomatosis.—Dr. W. G. DANGERFIELD.

Essential Hyperlipaemia and Primary Hypercholesterolaemia.—Dr. P. A. J. SMITH.

Familial Xanthomatosis.—Dr. J. N. HARRIS-JONES, Dr. E. GRAHAME JONES and Dr. P. G. WELLS.

NORTH BRITISH DERMATOLOGICAL SOCIETY.

Edinburgh, 13 December 1956.

Lymphocytic Infiltration of the Skin.—Dr. G. A. Grant Peterkin.

A woman, aged 76 years.

History.—The patient received an insect bite on the right cheek 3 years ago. A septic infection ensued and healed in 6 weeks. A month later a nodular eruption appeared on the injured site and has healed and recurred spontaneously. Itching was sometimes intense and exposure to sunlight appeared to aid healing.

Examination.—When first seen in April 1956 she presented a circinate plaque 3 cm. in diameter on the right cheek, consisting of domed indurated red nodules on a slightly atrophic skin. The picture was not that of a carcinoma, lupus erythematosus, Boeck's sarcoid or lupus vulgaris and the possibility of a fixed drug eruption was suspected. Tablets containing aspirin, phenacetin and codeine for rheumatoid arthritis were stopped for several weeks with no improvement.

Treatment.—Hydrocortisone ointment and x-ray (350 r)—no improvement.

Chloroquine sulphate, 0·2 g. night and morning, caused a marked improvement but had to be stopped because of confusion and claustrophobia. The pain of her rheumatoid arthritis was improved while she took chloroquine.

Biopsy (Dr. R. F. Ogilvie).—" The Malphighian layer of the epidermis is mostly thin and devoid of rete pegs, but shows thickening towards one end. The cornified layer is slightly thickened ; the superficial corium is oedematous, conspicuously infiltrated with round cells, mainly lymphocytes, and granulating. No evidence of neoplasm is present. The features are those of non-specific chronic inflammation with repair and reactive epidermal thickening."

Hypekeratosis Palmaris et Plantaris with Ainhum-like Constriction of the Toes.—Dr. P. W. Hannay.

Female, aged 36 years.

History.—She has suffered from tylosis of the palms and soles from the age of 3 months. It is only during the past few years that a constricting band of fibrous tissue has appeared around each of the 5th toes. The band around the right 5th toe became so tight that secondary sepsis kept recurring and was treated as a recurrent fungus infection. She was referred for an opinion 5 months ago when the present diagnosis was made and the toe was amputated. So far the left 5th toe has caused no discomfort. She originates from Orkney, as is so commonly found in these cases of congenital tylosis. No hyperidrosis, no ingestion of arsenic.

Family history.—Tylosis has been present for generations in her mother's family. Patient's own daughter appears to be unaffected. No family history of pseudo-ainhum.

Acrodermatitis Pustulosa Perstans.—Dr. G. A. Grant Peterkin.

A woman aged 54.

Family history.—Mother had rheumatoid arthritis and psoriasis.

History.—Two and a half years ago she developed an erythematous crusted and pustular eruption around the umbilicus which was treated with gentian violet without effect. Some months later she lacerated the tip of the right ring finger and a similar eruption appeared. This was treated by a surgeon as a perionychia with no improvement.

Since then numerous discoid lesions have appeared, almost all on the limbs, erythematous and studded with pustules which dry up to produce crusting and scaling. The pustules are small and discrete. The condition resembled pustular psoriasis.

Investigations.—Bacteriological examination : no growth on two occasions and a scanty growth of *Staphylococcus albus*, probably a commensal organism, on a third occasion.

Biopsy.—A superficial pustule situated in the upper rete. There is much spongiosis ; the pustule and surrounding epidermis contain many neutrophils. Compatible with the diagnosis of acrodermatitis pustulosa perstans.

Treatment.—Sulphonamides and antibiotics produced no improvement, for the pustules still appeared in crops. ACTH has controlled the eruption for some months ; present dose 20 i.u. daily plus Diodoquin, 4·2 g. daily.

The following cases also were shown :

Telangiectasia and Pigmentation. Porphyria Cutanea Tarda simulating Scleroderma.—Professor G. H. Percival.

Kerato-acanthoma and Self-healing Squamous Cell Carcinoma. Foreign-body Granuloma in Tattoo. Kyrle's Disease. Ocular Pemphigus. Cutis Hyperelastica.—Dr. G. A. Grant Peterkin.

Lichenoid Parapsoriasis. Epithelioma Adenoides Cysticum.—Dr. P. W. Hannay.

CORRESPONDENCE.

The Editor, ' British Journal of Dermatology '.

SIR,—Dr. A. Scott (p. 94) does well in calling attention to the important discrepancy which her recent investigation on " The Question of Urinary Hyperacidity in Seborrhoeic Dermatitis " has revealed. There was however no doubt of such an association when the late Dr. H. W. Barber and I published our article (*Brit. med. J.*, 1918, ii, 245) on the military disabilities occasioned by this disease during the Great War, 39 years ago. The great majority of our cases had been sent back more or less directly from the trenches, and many hundreds of them passed through our wards in No. 25 General Hospital, at Hardelot Plage. The clinical manifestations were invariably acute and bore little resemblance to the types commonly met with in civilian practice. Our observations were confirmed by the late Dr. H. MacCormac and other members of the medical staff, and I do not recollect any divergence from the hyperacidity pattern in these cases on admission. The speed of urinary response to the administration of alkaline mixtures to these patients varied considerably, as also did their clinical recovery.

Without attempting to elaborate on the metabolic and biochemical issues which were fully discussed in our article, a re-perusal of it has exposed a serious omission which, it seems to me, must weaken or invalidate some of the conclusions at which we arrived. *There is no record of urinary tests on controls*, and I suspect that most if not all of the casualties transferred from the line to the base would have demonstrated a similar hyperacid reaction in the urine. It would be reasonable to blame this on the " iron ration " universally allocated to all troops in the forward areas, so notoriously lacking in fresh vegetables, fruit and vitamins and overloaded with tinned meat, chocolate and biscuits. Such a diet would have tended to promote the urinary hyperacidity so consistently met with in our seborrhoeic cases, which we at the time, perhaps erroneously, regarded as a specific association.

I am, yours etc.,

H. C. SEMON.

Penn, Buckinghamshire,
April 1957.

CURRENT LITERATURE

THE USE OF ENDOCRINES IN DERMATOLOGY. R. L. Cormie and J. Sommerville. (1956) *Med. Pr.*, **236**, 383.

The role of each of the secretions of the ductless glands is briefly outlined.

In dermatology the only endocrine secretions with any great therapeutic value are the corticosteroids. The present position with regard to the systemic and local use of these substances is adequately covered, proper stress being laid on their dangers.

Although sex hormones are also used occasionally in dermatology, such use is very limited.

H. R. V.

HYDROCORTISONE COMBINED WITH ANTIBIOTIC IN TOPICAL THERAPY. R. W. Carslaw. (1956) *Med. Pr.*, **235**, 542.

With the availability of hydrocortisone on a general practitioner's prescription, such preparations will be extensively used as antipruritics. The author has treated an admittedly small number of cases with various preparations containing hydrocortisone and 9-α-fluorohydrocortisone acetate alone and in combination with terramycin and graneodin ointment.

In addition, a small trial was made with 9-α-fluorohydrocortisone and 1% crude coal tar.

These preparations are valuable in that treatment time is reduced, but specific therapy where available must also be used.

H. R. V.

RECURRENT BOILS. G. Hodgson. (1956) *Med. Pr.*, **236**, 62.

Pyogenic staphylococci are commonly present on normal skin and for boils to develop, the natural resistance of the skin to this infection must be lowered. This state may occur in the moist sweating alkaline areas of the axillae and groins, after the use of wet hot fomentations, in association with being "run down" and at times of emotional stress. The actual biochemical cause may be related perhaps to some change in the fatty acid secretion or in the water balance of the skin. Recurrent boils therefore, occur from repeated staphylococcal infection and a breakdown of the skin immunity.

Treatment is designed to localize or abort the infection and to avoid measures that may damage or produce sensitization dermatitis in the skin. The skin around the boil can be sterilized with paints such as tincture of iodine in spirit, 1 in 10 magenta paint, B.P.C. gentian violet 1% in spirit and brilliant green 1% in spirit. Antibiotics may be used to control acute severe furunculosis; penicillin is still the best and cheapest, although penicillin-resistant organisms are increasingly common.

The treatment of boils in specific areas such as the face, axillae, groins, eyelids, ears, etc. is given in detail, and in chronic furunculosis treatment of the background cause and prevention of re-inoculation is very important. This is given in full, ending with such measures as the use of colloidal manganese, autohaemotherapy and tin.

H. R. V.

THE CLINICAL SIGNIFICANCE OF PIGMENTATION OF THE SKIN. A. Lyall and A. Lyell. (1956) *Med Pr.*, **235**, 481.

A comprehensive summary is given of the conditions associated with alteration in skin colour. Addison's disease is particularly stressed since it responds so well to modern treatment.

Other conditions briefly discussed are haemochromatosis, the colour changes of hypercholesterolaemia, carotinaemia and xanthoma, myxoedema, ingestion of oranges in excess and mepacrine, nutritional deficiencies and Hodgkin's disease. Localized pigmentation is seen in sunbathers, pitch workers, as a result of some cosmetics, arising from exposure to heat, chloasma and freckles, moles and seborrhoeic warts, following scarring and healed dermatoses, leprosy and various drug eruptions. Comprehensive list indeed but there is no clue given of the mechanism underlying their changes.

H. R. V.

BALDNESS. E. J. Moynahan. (1956) *Med. Pr.*, **236**, 87.

This most comprehensive article covers the subject from the embryological and phylogenetical considerations of hair formation to the effects produced on the hair by nuclear weapons. The congenital alopecias are classified clinically and illustrated, the hereditary factors are briefly discussed and the non-cicatrical and cicatrical alopecias are listed and described giving appropriate treatment when available.

Many widely-held ideas such as frequent cutting strengthening the hair, vigorous massage promoting growth and singeing being beneficial are " de-bunked ". H. R. V.

CROSS SENSITIVITY BETWEEN NICKEL AND COPPER. S. Epstein. (1955) *J. invest. Derm.*, **25**, 269.

The author fails to find support for the observation by Everall *et al.* that nickel-sensitive persons are often allergic to chrome; and he attributes the error to the use of too strong (2·6%) a solution of chrome.

But in his own demonstration of cross sensitivity between nickel and copper he does not hestitate to use 10% solutions for patch testing. He urges that divalent copper be regarded as belonging to the " transitional " group VIII of the periodic system with iron cobalt and nickel.

J. H. T. D.

EXPERIMENTAL STRESS DERMATITIS. J. Kramar, V. W. Meyers and C. M. Wilhelmj. (1955) *J. invest. Derm.*, **25**, 275.

One hundred and ninety-six out of 313 rats and 15 out of 20 guinea-pigs developed eczematide-like lesions on exposure to stress (cold, fasting followed by gorging, etherization, compulsory swimming, an incision, or the crushing of one hind leg); 27 rats and 4 guinea-pigs served as controls. [Since it is stated that these animals had to be carefully trained not to mind being strapped to a board one hopes there was no conscious selection; and in any case one wonders if there was a sufficient number in the control series.] The development of these lesions and their extent was closely associated with certain changes in capillary resistance constituting a response to trauma that has already been reported elsewhere by the first author.

The suction cup used for measuring capillary resistance plus the preparation of the skin may have helped to elicit the lesions all of which occurred in the neighbourhood of the testing, but since it was ineffective in unstressed animals it is necessary to postulate an endogenous factor which may well be identical with that responsible for the reduction of capillary resistance.

In view of these observations and the demonstration in another work by the first author that corticosteroids raise capillary resistance and somatotropic hormone lowers it, it is suggested that the intrinsic factor in eczema may be an endocrine imbalance.

[Anything that might offer physiological respectability to " nerve rashes " is of course welcome but we do not often hear of eczema following surgical operations or in Channel swimmers.]

J. H. T. D.

ELECTRON MICROSCOPY OF COLLAGEN FIBRES DURING CORTISONE THERAPY OF ALOPECIA TOTALIS (TECHNICAL PROBLEMS). R. A. Wilson, J. L. Danto and S. Maddin. *J. invest. Derm.*, **25**, 175.

Showed no alteration in the physical structure of collagen fibrils in total alopecia either before or during treatment with cortisone. J. H. T. D.

THE ABSENCE OF THE APOKRINE GLANDS AND HAIR IN THE AXILLA IN MONGOLISM AND IDIOCY. W. B. Shelley and T. Butterworth. (1955) *J. invest. Derm.*, **25**, 165.

Since all 7 subjects had reasonably normal menstrual cycles it is presumed that ovarian hormone plays no primary role in the development of axillary hair and apokrine glands. Eccrine glands were also undeveloped. J. H. T. D.

THE EFFECT OF ORDER OF DRUG ADMINISTRATION AND REPEAT PLACEBOES ON THE GALVANIC SKIN RESISTANCE IN HUMAN SUBJECTS. D. J. Perry, G. E. Mount, C. D. Hull and R. H. Zeillenger. (1956) *J. invest. Derm.*, **25**, 179.

This was a control study designed to check the validity of an earlier finding that atropine alters the G.S.R. It might well be taken as a model for thoroughness as well as an indication to clinical experimenters of the multiplicity of the pitfalls. J. H. T. D.